

Ser. No. 10/675,444  
Atty. Docket No. 103-001PUS  
Amendment in Response to Final Office Action Dated October 16, 2008

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### REMARKS

Claims 1, 4-12, 14-19 and 21-25 are pending in the application. In the present submission, no claim is amended, thus precluding any new matter concerns.

#### **I. Telephonic Interview of January 8, 2009**

A telephonic interview regarding the instant application took place on January 8, 2009, with Examiner Dr. Louise Humphrey and the Supervisory Patent Examiner, Dr. Bruce Campell. The substantive content of this conversation is embodied in "APPLICANTS' SUMMARY OF THE SUBSTANCE OF THE INTERVIEW" which was submitted to the U.S. PTO on February 2, 2009 pursuant to §§ 37 C.F.R. 1.2, 1.133 and MPEP 713.04, herein incorporated by reference, and will be addressed in the following Remarks.

#### **II. Rejection of Claims 1, 4-8, 10, 15-19, 24 and 25 Under 35 U.S.C. § 103(a) in view of Tobiasch and Snijder**

Claims 1, 4-8, 10, 15-19, 24 and 25 stand rejected as being unpatentable over Tobiasch *et al.*, (2001) ("Tobiasch") in view of Snijder *et al.* (1999) ("Snijder"). Applicants respectfully traverse this rejection.

Applicants wish to point out, commensurate with our arguments already of record, that Tobiasch describes a plurality of different DNA vaccine compositions, for example, cDNA sequences derived from EAV ORF 3, ORF 4, ORF 5, and ORF 7 which were cloned into expression vectors pCR3.1, pDisplay, and/or pcDNA3.1/HisC for the purposes of inducing an immune response by vaccination that could prevent EAV. The Examiner indicates that Tobiasch teaches prevention of EAV in horses by DNA vaccination (Office Action, page 5). However, Applicants respectfully point out that Tobiasch in fact conducts all of the vaccination experiments using Balb/c mice (e.g. on page 191, 2<sup>nd</sup> col.; Table 2 on page 195; Figure 5 on page 197 and in the Title) and only *posits* that "[t]hese results obtained from these studies justified proofing the capability of the EAV cDNA sequences of the viral genes ...in horse" (Abstract). However, Tobiasch does not actually carry out these experiments, thus no firm conclusions of how the Tobiasch vaccine would function in horses can be drawn.

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The Examiner acknowledges that Tobiasch does not disclose EAV ORF 2 in the vaccine compositions (Office Action, page 5). To satisfy this deficiency, the Examiner refers to Snijder, who “discloses EAV ORF 2, which contains the genes ORF 2a and ORF 2b”... which are said to be “essential for the production of infectious progeny virus” (Office Action, page 6; emphasis added). In addition, the Examiner asserts that because Snijder discloses “that ORF 2a is conserved in all *Arteriviruses*” (Office Action, page 6), it would have been obvious for the skilled person to modify the teachings of Tobiasch to simply introduce the “conserved” ORF 2 into the Tobiasch composition to achieve a vaccine having a broad-range immune response against all *Arteriviruses*. Applicants respectfully disagree with this assessment.

The teachings of Tobiasch, and deficiencies thereof, are explained above; other arguments by Applicant concerning why this disclosure is not relevant to the patentability of the instant invention are already of record.

The Snijder disclosure provides the identification of ORF 2a in the EAV genome, wherein the EAV ORF 2a (corresponding to an envelope protein, E) is thought to be “conserved in all *Arteriviruses*” (Abstract). However, as discussed in the Examiner Interview on January 8, 2009, Snijder admitted that this E protein appears to be susceptible to various post-translational modifications, which “could have many implications for E-protein function, in terms of both protein-lipid and protein-protein interactions” that can “play a role in virus particle formation, receptor recognition, virion stability, and virus disassembly” (page 6344, left-hand column; and please see the “Declaration” by Dr. Giese at ¶15). This admission undoubtedly has consequences for developing vaccines containing ORF 2a, since the skilled person must correctly identify *which* form of ORF 2a would be suitable for developing a vaccine composition, such that eliciting the desired immune response can be done in a predictable fashion (i.e. overcoming the above-stated implications of any post-translational modification of ORF 2a), without incurring any harmful side effects to the subject receiving the vaccine.

Furthermore, Snijder makes clear that selecting the correct combination of EAV ORF sequences for invoking an immune response requires further investigation. For example, Snijder states that “the simultaneous expression of EAV ORFs 2a, 5, and/or 6 in vaccinia virus-based expression systems **did not result** in the production of subviral particles...” and may require “the expression of additional viral genes” (page 6344, right-hand column; emphasis added). But, which genes? Other ORF sequences? Alternative (post-translational) forms of the ORF 2a? For

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Snijder, this remained an open question. If, for example, we were only to consider the EAV ORF sequences alone (i.e. 'mixing and matching' to arrive at an acceptably immunogenic EAV ORF sequence combination): Tobiasch describes ORFs 3, 4, 5, and 7, while Snijder describes ORF 2a and ORF 2b, which collectively provides 6 different ORF sequences. In addition, Snijder, in FIG. 3, indicates that the EAV ORF genome has 7 different ORFs. Arguably, the skilled person, attempting to assemble an immunogenic composition containing EAV ORF sequences, would be confronted with 8 different ORF sequences (ORF 2 offers 2a and 2b), meaning a total of 40,320 possible combinations (using a factorial analysis). Arguably, the skilled person has some work to do in order to arrive at the vaccine compositions disclosed by the instant invention.

We respectfully refer the Examiner to the Declaration submitted herein by Dr. Giese, as a whole, as objective evidence for factually supporting the present arguments of counsel.

As described previously, the instant invention relates to a therapeutic composition capable of preventing or treating an EAV-associated condition, and provides a nucleic acid-based prophylactic or therapeutic vaccine (and methods of use) for EAV-associated diseases. In a first important embodiment, the invention relates to a vaccine composition which is protective against equine *Arterivirus* (EAV) infections in horses and induces a cellular immune response, consisting of EAV open reading frame nucleic acids (ORF) 2, SEQ ID NO:5, SEQ ID NO:9 (ORF 5), and SEQ ID NO:7 (ORF 7) (recited by claims 1 and 15).

We note that the Examiner has acknowledged that the Tobiasch disclosure (cited as the "closest prior art" in the various §103 combinations) is silent with respect to the inclusion of ORF 2 in a vaccine, said ORF 2 being "indispensable for the generation of infectious virus particles" according to Snijder (page 6336, bottom of 1<sup>st</sup> col.). Thus it is not clear how the Tobiasch compositions, without the "indispensable" ORF 2 sequence, could produce infectious viral progeny.

Notwithstanding the absence of the ORF 2 in the Tobiasch vaccine, the Examiner states that because ORF 2 is in the same reading frame as ORF 5 and ORF 7 and that ORF 2a is highly conserved in all *Arteriviruses*, the skilled person would have a reasonable expectation of success of eliciting a sufficient immune response against *any* strain of *Arteriviruses*. However, we respectfully submit that just because the ORF 2 sequence is conserved, even highly conserved, does not mean that the skilled person would automatically expect this sequence to elicit a measurable protective immune response, such as the response observed for the highly

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immunogenic ORF 5 (Chirnside, of record). This reasonable expectation of success is also questionable, since the ORF 2 sequence only makes up 1-2 % of the *entire* EAV genome, thus its ability to mobilize a significant immune response would not be guaranteed nor expected. Accordingly, this uncertainty would not encourage the skilled person to consult the Tobiasch disclosure as a starting point for arriving at the vaccines disclosed by the presently claimed invention (see, e.g. Declaration at ¶ 12).

The naturally low occurrence of the EAV ORF 2 antigen concentration was thought by scientists in this field to contribute to the extremely poor antigenic recognition of the ORF 2 encoded protein, i.e. only providing a limited antibody response as observed in one mouse B-cell model (Chirnside, of record). This observation may explain why, until now, the use of ORF 2 in a vaccine composition has not been pursued. This, in part, explains Applicant's statement in [0057], where the use of a vaccine comprising EAV ORFs 2 + 5 + 7 to elicit a significant and sustainable response (e.g. in Table 17 and Tables 19-20) was "surprising" and "contrary to the opinion in the art" than when the entire EAV cDNA sequence was used (e.g. Chirnside) (please see Declaration at ¶ 13).

Another unexpected aspect of the invention was that ORF 7 is recognized by cytotoxic T-cells (since the ORF 7 protein induced a cellular immune response, e.g. see Tables 19 and 20), since this ORF encodes for an internal capsid protein *within* the virus. As stated in the Declaration at ¶ 14, this unexpected recognition by, and thus mobilization of, the T-cell response to the ORF 7 antigen may be due to imperfect translation of the mRNA to protein during the viral replication process, which provokes this cellular immune response due to mistakes in the capsid protein assembly.

Consequently, independent claims 1 and 15 (and all associated-dependent claims and independent claims reciting the features thereof) are not *prima facie* obvious over Tobiasch in view of Snijder, at least because: neither of these references, alone or in combination, teach or suggest a vaccine composition or a nucleic acid vector (or methods of use) consisting of nucleic acid(s) encoding a combination of EAV ORF 2, ORF 5 and ORF 7; *nor* that this particular ORF combination induces both a neutralizing antibody response and a cytotoxic T cell response against EAV infection in the manner described by the present invention.

Accordingly, since *prima facie* obviousness has not been established, Applicant respectfully requests that the present rejection under §103(a) be reconsidered and withdrawn.

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**III. Rejection of Claims 1, 4-12, 15-19, 24 and 25 Under 35 U.S.C. § 103(a) in view of Tobiasch, Snijder and Krieg**

Claims 1, 4-12, 15-19, 24 and 25 stand rejected as being unpatentable over Tobiasch in view of Snijder and Krieg *et al.* (1998) ("Krieg"). Applicants respectfully traverse this rejection.

The teachings of Tobiasch and Snijder are set forth above. As discussed, both of these publications fail to disclose or even suggest the teachings of the instant invention, namely, the advantageous EAV ORF vaccine combinations, and its desirable impact on both the humoral and cellular immune response, which affords optimal immunization against infection upon EAV exposure, as Applicant explains in §II, *supra*. Moreover, as is noted in the Office Action on page 7, neither citation "discloses any adjuvant in the vaccine composition".

The Examiner observes that Krieg suggests "unmethylated CpG dinucleotides as adjuvant for DNA vaccines" in order to "enhance the Th1 immune response" and furthermore, that "IL-2" improves activation of antibody-dependent cellular cytotoxicity" (Office Action, page 7).

Since the Tobiasch and Snijder disclosures, alone or in combination with publicly available knowledge at the documented invention date, do not result in the foundational compositions or methods of any of the pending claims, the Krieg approach can not be reasonably found to inspire the skilled person to implement a variation, i.e. adding CpG dinucleotides and/or IL-2 to the "DNA vaccine composition of Tobiasch" in order to arrive at the same vaccine compositions, having the same immunogenic activity, as presently claimed—given that the Tobiasch and Snijder disclosures either fail to describe the use of the ORF 2 and/or provide any information regarding its possible cytotoxic activity upon exposure to the EAV virus (see also, e.g. Declaration at ¶¶11-12 and ¶15).

Since *prima facie* obviousness has not been established, Applicant respectfully requests that the present rejection under §103(a) be reconsidered and withdrawn.

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**IV. Rejection of Claims 1, 4-10, 12, 15-19, 24 and 25 under 35 U.S.C. § 103(a) in view of Tobiasch, Snijder and Cantlon**

Claims 1, 4-10, 12, 15-19, 24 and 25 were rejected as being unpatentable over Tobiasch in view of Snijder and Cantlon *et al.* (2000) ("Cantlon"). Applicants respectfully traverse this rejection.

The teachings of Tobiasch and Snijder are set forth above. As discussed, both of these publications fail to disclose or suggest the teachings of the instant invention, namely, the advantageous EAV ORF vaccine combinations and its desirable impact on both the humoral and cellular immune response, which affords optimal vaccination against infections caused by EAV exposure, as Applicant explains in §II, *supra*. Furthermore, the Examiner notes that neither of these references disclose "IL-2 in the EAV vaccine composition" (Office Action, page 8).

The Examiner states that Cantlon teaches that "in mice, co-administration of a plasmid that expressed IL-2 resulted in a significant, though modest, increase in antibody titers" (Office Action, page 8) (emphasis added).

Since the Tobiasch and Snijder disclosures, alone or in combination with publicly available knowledge at the documented invention date, do not result in the foundational compositions or methods of any of the pending claims, the Cantlon approach can not be reasonably found to motivate the skilled person to implement a variation, i.e. adding IL-2 to the vaccine compositions taught by these references in order to arrive at the same vaccine compositions, having the same immunogenic activity as those presently claimed—since the Tobiasch and Snijder disclosures either fail to describe the use of the ORF 2 and/or provide any information regarding its possible cytotoxic activity upon exposure to the EAV virus (see also, e.g. Declaration at ¶11-12 and ¶15).

Since *prima facie* obviousness has not been established, Applicant respectfully requests that the present rejection under §103(a) be reconsidered and withdrawn.

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**V. Rejection of Claims 1, 4-8, 10, 14-19, 24 and 25 Under 35 U.S.C. § 103(a) in view of Tobiasch, Snijder and Gregoriadis**

Claims 1, 4-8, 10, 14-19, 24 and 25 were rejected as being unpatentable over Tobiasch in view of Snijder and Gregoriadis *et al.* (1997) ("Gregoriadis").

The teachings of Tobiasch and Snijder are set forth above. As discussed, both of these publications fail to disclose or suggest the teachings of the instant invention, namely, the advantageous EAV ORF vaccine combinations and its beneficial impact on mobilizing both the humoral and cellular immune response, thus providing optimal immunization against infections upon EAV exposure, as Applicant explains in §II, *supra*. Furthermore, the Examiner notes that these references also fail to disclose "encapsulating the nucleic acid or vector vaccine into cationic liposomes" (Office Action, page 8).

The Examiner explains that Gregoriadis discloses that "antigen-coding vector entrapped into cationic liposomes leads to greatly improved humoral and cell-mediated immunity" (Office Action, page 9).

Since the Tobiasch and Snijder disclosures, alone or in combination with publicly available knowledge at the documented invention date, do not result in the foundational compositions or methods of any of the pending claims, the Gregoriadis approach can not be reasonably found to motivate the skilled person to implement a variation, i.e. encapsulating the nucleic acids or vector vaccines taught by these references into cationic liposomes to thus arrive at the same vaccine compositions having the same immunogenic activity as those presently claimed—given the deficiencies of the Tobiasch and Snijder disclosures as noted above (see also, e.g. Declaration at ¶11-12 and ¶15).

Since *prima facie* obviousness has not been established, Applicant respectfully requests that the present rejection under §103(a) be reconsidered and withdrawn.

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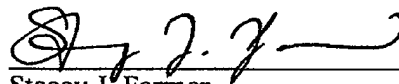
**IX. CONCLUSION**

In view of arguments set forth above, Applicants kindly submit that the rejections contained in the Office Action mailed on October 16, 2008 have been overcome, and that the pending claims are in good condition for grant. Accordingly, we request that the Examiner issue a notification of allowance.

Applicants presently enclose a Petition for an "Extension for Response within Third Month" (small entity). Please charge the \$555.00 fee as set forth in Fee Code 2253 per 37 C.F.R. 1.17(a)(3), which is submitted herewith on enclosed Form PTO-2038. No other fees are believed to be due in connection with this correspondence.

If the Examiner believes that a telephone call would expedite the allowance of the present case, the Examiner is respectfully requested to contact Applicant's undersigned attorney at the number indicated below.

Respectfully submitted,

Dated: April 2, 2009  
Stacey J. Farmer  
Reg. No. 42,526

Customer No. 67304

GRUND INTELLECTUAL PROPERTY GROUP  
Nikolaistrasse 15  
D-80802 Munich  
GERMANY

+ 49 (89) 54 80 19 - 0 (telephone)  
+ 49 (89) 54 80 19 - 10 (facsimile)  
[farmer@grundipg.com](mailto:farmer@grundipg.com) (email)



## ANNEX A

### DNA VACCINATION OF HORSES

Detection of EAV-specific antibodies: In order to demonstrate the expression of EAV cDNA ORF2 in the autologous animal system horse, it was necessary to screen the horse sera prior to immunization trial. The selection of the suitable animals was based on the results obtained from the analysis of the horse sera. Characteristics of the horses are summarized in TABLE 1. These studies allowed detecting the existence of a previous naturally occurring EAV infection in horses.

The horse sera were analyzed by neutralization assay and ELISA as described above. Serum was collected 9 days, before the initial immunization and investigated at the Vet-Med-Laboratory in Ludwigsburg, Germany. The results are summarized in TABLE 1.

TABLE 1 Characteristics of the horses involved in this study

HORSE	RACE	AGE	SEX	NT-TITER
1 (MAISJE)	Warmblood	14 yrs	mare	<1:2
2 (RUDI)	Warmblood	1 year	gelding	<1:2

Immunization of the horses: Two horses were immunized by intramuscular (i.m.) injection of the EAV plasmid DNA encoding ORF 2. The i.m. inoculations were applied to the musculus semimembranosus/semitendinosus/gluteus. A detailed protocol of the DNA immunization (including, amount of DNA, adjuvants, buffers) is provided in TABLE 2. None of the animals developed fever and the local reactions.

TABLE 2 Immunization protocol: Intramuscular immunization (i.m.) schedule with the cDNA EAV ORF 2 and with cDNA encoding equine IL 2.

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HORSE	FIRST IMMUNIZATION (10-02-2001)	BOOSTER (10-30-2001)	BOOSTER (11-28-2001)
1 (MAISJE)	1000 µg ORF2 and 1000 µg IL-2	1000 µg ORF2 and 1000 µg IL-2	1000 µg ORF2 and 1000 µg IL-2
2 (RUDI)	1000 µg ORF2 and 1000 µg IL-2	1000 µg ORF2 and 1000 µg IL-2	1000 µg ORF2 and 1000 µg IL-2

Collection of blood and serum samples: Peripheral blood lymphocytes, serum and plasma of the horses were taken as outlined in TABLE 3. Up to date, blood and serum samples were taken nine times after the 2<sup>nd</sup> booster immunization to measure the kinetics of antibody titers and activities of cytotoxic T-lymphocytes. The antibody titers following vaccination are given in TABLE 4.

TABLE 3: Sample collection and immunization strategy

IMMUNIZATION STAGE	DNA APPLICATION	COLLECTION OF PLASMA SAMPLES	ISOLATION OF PBMC*
Pre-immunization	n.d.	09-24-2001	09-24-2001
Basic immunization	10-02-2001	n.d.	n.d.
1. Booster	30-10-2001	11-02-2001	11-02-2001
2. Booster	11-28-2001	11-27-2001	11-27-2001
		12-06-2001	12-06-2001
		12-27-2001	12-27-2001
		02-04-2002	
		02-27-2002	
		03-26-2002	
		04-20-2002	
		05-29-2002	

\* peripheral blood mononuclear cells; n.d.: not done

## ANNEX A

TABLE 4 Results of neutralization tests (NT) in which sera of two horses, Horse 1 (Maisje) and Horse 2 (Rudi), were screened for the detection of neutralizing antibodies against EAV following DNA vaccination with cDNA of EAV-ORF2 and equine interleukin 2 (IL-2).

IMMUNIZATION SCHEDULE:	NT-Titer:	
	Horse 1 (Maisje)	Horse 2 (Rudi)
1.Co-serum: 09-24-2001	<1:2	<1:2
<i>Vaccination</i>		
1.PV-serum: 11-02-2001	<1:2	<1:2
2. PV-serum: 11-27-2001	1:128	1:32
3. PV-serum: 12-06-2001	1:32	1:96
4. PV-serum: 12-27-2001	1:128	1:128
5. PV-serum: 02-04-2002	1:128	1:128
6. PV-serum: 02-27-2002	1:128	1:128
7. PV-serum: 03-26-2002	1:64	1:96
8. PV-serum: 04-30-2002	1:128	1:32
9. PV-serum: 05-29-2002	1:128	1:96

Co-Serum: control serum prior to vaccination

PV-serum: post vaccination serum after vaccination

Cytotoxic T-cell reactions of the horses against EAV after DNA vaccination: The immunological methods are mostly based on standard protocols of Current Protocols in Immunology (1997) and modifications of published protocols (Allen *et al.*; J. Virol. 1995, 69, 606-612; Niewiesk *et al.*, J.Virol. 1993, 67, 75-83; Baker *et al.*, J.Immunol.1999, 162, 4496-4501).

Target cells: Autologous mononuclear blood cells were isolated from fresh blood prior vaccination and purified via Percoll gradient (60%, Pharmacia) and

## ANNEX A

irradiated with 300 Gy-Cobalt. The cells were cryopreserved in fluid nitrogen at a concentration of  $5 \times 10^6$  cells/ml in a specific cryomedium (45% RPMI 1640, 45 FCS, 10% DMSO).

After three washing steps in PBS, the mononuclear cells were incubated with EAV at a M.O.I. (multiplicity of infection) of 1 for four hours/ $37^\circ$  C, washed with PBS and then ready for stimulation.

Stimulation: A three times amount of non-irradiated lymphocytes (effector cells) as responder cells ( $3 \times 10^6$  stimulator cells and  $1 \times 10^7$  responder cells) were taken for stimulation. Activation was supported by IL-2, 5% ConcavalinA (ConA) or  $3\mu\text{g}$  Pokeweed-Mitogen (PWM)/ $10^7$  cells. The activated T-lymphocytes (effector cells) were isolated by Percoll gradient (60%) after five to six days of incubation with the stimulator cells.

Chromium-Release-Assay: Target cells were infected with EAV M.O.I.10 overnight. The cells were then incubated with  $3.7 \text{ MBq Na}^{51}\text{CrO}_4$  (Amersham) / $10^6$  cells/ $37^\circ$  C/90min. After two washing steps with PBS ( $400 \times \text{g}/22^\circ$  C/5 min)  $10^4$  target cells/50  $\mu\text{l}$ /well were plated on a microtiter plate. An aliquot of cells was taken in order to measure the uptake of  $^{51}\text{Cr}$  (0.3-2.2 cpm/cell). The spontaneous release of  $^{51}\text{Cr}$  and the maximum of release, total release, by adding 2.5% TritonX100 was tested by triplicate measurements in each test. The activated T-lymphocytes (CTLs), effector cells, were added to the  $^{51}\text{Cr}$  labeled target cells, the microtiter plates were centrifuged ( $150 \times \text{g}/22^\circ$  C/2 min) and then incubated ( $37^\circ$  C/5 %  $\text{CO}_2$ /6 hr). Tests were performed in duplicate. The cells were then centrifuged ( $600 \times \text{g}/5 \text{ min}$ ), and the released radioactivity in 75 ml supernatant was measured using a gamma counter (Wallac 1450).

Calculations of cell-lysis: The specific lysis of the target cells were calculated according to the following standard formula:

$$\text{Specific lysis (\%)} = (a-b) / (c-b) \times 100$$

- a: release/cpm of combined effector and target cells
- b: spontaneous release/cpm of the target cells
- c: maximum release/cpm of the target cells

## ANNEX A

The spontaneous release (b) was in the range of 37 +/- 6 %. The maximum of release (c) was of in the range of 95 +/-3 %. The Student T-test was used for calculation of the specific lysis. The results of the cytotoxic T-cell reactions of the horses against EAV after DNA vaccination are given in TABLES 5 and 6.

TABLE 5: Cytotoxic T-cell reactions of Horse 1 (MAISJE)

HORSE 1 (MAISJE)	Effector Cell : Target Cell at a ratio of 1:	1. TEST: 10-01-01 (in cpm)	2. TEST: 11-07-01 (in cpm)	3. TEST: 12-06-01 (in cpm)	4. TEST: 01-08-02 (in cpm)
	100	-	-	25	32
	50	2	15	20	35
	25	0	4	8	30
	12.5	0	0	6	12

TABLE 6: Cytotoxic T-cell reactions of Horse 2 (RUDI)

HORSE 2 (RUDI)	Effector Cell : Target Cell at a ratio of 1:	1. TEST: 10-01-01 (in cpm)	2. TEST: 11-07-01 (in cpm)	3. TEST: 12-06-01 (in cpm)	4. TEST: 01-08-02 (in cpm)
	100	-	-	10	14
	50	8	6	16	12
	25	4	5	12	9
	12.5	2	2	7	7